Fetal release of copeptin in response to maternal oxytocin administration: a randomized controlled trial

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Abstract: OBJECTIVE: To test whether an oxytocin challenge test raises neonatal levels of copeptin, the C-terminal portion of proarginine vasopressin, a sensitive stress marker elevated in neonates born by vaginal delivery as opposed to elective cesarean delivery. METHODS: In a randomized controlled trial in women with a singleton pregnancy undergoing elective cesarean delivery at greater than 36 weeks of gestation and no contractions or rupture of membranes, we compared arterial umbilical cord plasma concentrations of copeptin between neonates exposed to an oxytocin challenge test before elective cesarean delivery and those administered saline infusion (placebo group). Women randomized to an oxytocin challenge test received 5 international units/500 mL oxytocin Ringer lactate infused at a rate of 12 mL/h and doubled every 10 minutes until it induced three uterine contractions per 10-minute interval, at which point it was discontinued. Neonatal copeptin levels were the primary endpoint. Secondary endpoints included biochemical and physiologic parameters of fetal and maternal well-being. RESULTS: From January 2012 to October 2012 and from September 2013 to January 2015, 78 women underwent an oxytocin challenge test and 78 placebo infusion, of whom 12 and 11, respectively, were excluded as a result of insufficient blood sample volume for analysis. Umbilical cord plasma copeptin levels [median (range)] were higher in neonates who underwent an oxytocin challenge test than those who underwent placebo infusion: 22.2 (3.22-2,319) compared with 7.39 (2.5-344.6) pmol/L (P<.001). There were no statistically significant differences between the two groups in secondary outcomes. CONCLUSION: Oxytocin challenge test-induced contractions before elective cesarean delivery trigger fetal copeptin release. CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, https://clinicaltrials.gov, NCT01962701.

DOI: https://doi.org/10.1097/AOG.0000000000001594

Original Research

Fetal Release of Copeptin in Response to Maternal Oxytocin Administration

A Randomized Controlled Trial

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OBJECTIVE: To test whether an oxytocin challenge test raises neonatal levels of copeptin, the C-terminal portion of proarginine vasopressin, a sensitive stress marker elevated in neonates born by vaginal delivery as opposed to elective cesarean delivery.

METHODS: In a randomized controlled trial in women with a singleton pregnancy undergoing elective cesarean delivery at greater than 36 weeks of gestation and no contractions or rupture of membranes, we compared arterial umbilical cord plasma concentrations of copeptin between neonates exposed to an oxytocin challenge test before elective cesarean delivery and those administered saline infusion (placebo group). Women randomized to an oxytocin challenge test received 5 international units/500 mL oxytocin Ringer lactate infused at a rate of 12 mL/h and doubled every 10 minutes until it induced three uterine contractions per 10-minute interval, at which point it was discontinued. Neonatal copeptin levels were the primary endpoint. Secondary endpoints included biochemical and physiologic parameters of fetal and maternal well-being.

RESULTS: From January 2012 to October 2012 and from September 2013 to January 2015, 78 women underwent an oxytocin challenge test and 78 placebo infusion, of whom 12 and 11, respectively, were excluded as a result of insufficient blood sample volume for analysis. Umbilical cord plasma copeptin levels [median (range)] were higher in neonates who underwent an oxytocin challenge test than those who underwent placebo infusion: 22.2 (3.22–2,319) compared with 7.39 (2.5–344.6) pmol/L ($P<.001$). There were no statistically significant differences between the two groups in secondary outcomes.

CONCLUSION: Oxytocin challenge test-induced contractions before elective cesarean delivery trigger fetal copeptin release.

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(Obstet Gynecol 2016;128:699–703)

DOI: 10.1097/AOG.0000000000001594

See related editorial on page 685.

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Supported by the Zurich Center for Integrative Human Physiology (ZIHP), University of Zurich, Zurich, Switzerland. S.W. was supported by a Swiss National Science Foundation Career Award for Medical Scientists (33CM30-124101).

Presented at the 1st Congress of joint European Neonatal Societies (jENS 2015), September 16–20, 2015, Budapest, Hungary.

The authors thank Beata Jaworek for technical assistance. The authors acknowledge their debt to the important intellectual input provided at the initiation of this trial by Prof. Ernst Beinder, who died in January 2016.

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Financial Disclosure

The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/16

Copeptin is a nonspecific but highly sensitive plasma indicator of stress and a more sensitive marker than cortisol.[1,2] It derives from the prohormone of arginine vasopressin (AVP) and is secreted in equimolar amounts to AVP from the pituitary into the circulatory system.[3] Pulsatile secretion, platelet binding, and a short half-life make direct measurement of AVP unfeasible in the clinical setting. Copeptin, however, remains stable in blood collection tubes and can readily be measured by sandwich immunoassay.[4]

Vaginal delivery of a healthy newborn provokes a unique surge in copeptin plasma concentration incommensurable with child or adult levels measured in any other situation.[5–8] In contrast, newborns delivered by elective cesarean delivery without preceding labor have low copeptin concentrations at birth unless

other stressors are present, including chorioamnionitis or fetal growth restriction.[7,9] In newborns delivered by cesarean delivery after the onset of labor, copeptin concentrations fall between these two extremes.[5,10]

The specific stressors inducing copeptin release during vaginal delivery remain unknown. Brief episodes of hypoxia suffice to trigger copeptin release in vivo.[11,12] Such episodes are occasionally observed during labor where they manifest as late decelerations on the cardiotocogram. However, in the absence of an abnormal or indeterminate cardiotocogram, hard evidence is lacking that labor per se causes a fetal stress response.

We conducted a prospective, randomized controlled trial in women scheduled for elective cesarean delivery to test whether the mild labor–no more than three contractions within 10 minutes–induced by an oxytocin challenge test suffices per se in the absence of any other identified stressor, in particular hypoxia, to raise neonatal copeptin levels.

MATERIALS AND METHODS

Enrollment ran from January through October 2012 and from September 2013 through January 2015. The institutional review board approved the study provided safety was assessed after enrolling 30 patients per group. No safety issues were detected and enrollment continued. The trial was registered at ClinicalTrials.gov, number NCT01962701.

The inclusion criteria were singleton pregnancy, elective cesarean delivery without preceding contractions or rupture of the membranes after completed 36 weeks of gestation, and absence of a contraindication to oxytocin. Exclusion criteria in the fetus were chromosomal aberration, malformation, fetal growth restriction, placenta previa, and infection. Maternal exclusion criteria were substance abuse, infection, hypertension, preeclampsia, diabetes type I or II, and autoimmune disease (eg, antiphospholipid syndrome, renal disease, or a history of more than one previous cesarean delivery). No mother in either group had received nonsteroidal anti-inflammatory drugs or vasoactive drugs during pregnancy.

The day before undergoing elective cesarean delivery, all eligible women were asked for their informed consent. On the day of elective cesarean delivery, after admission to the delivery room and placement of an intravenous line, women were randomized in a one-to-one ratio using a random number generator to infusion of either oxytocin (oxytocin challenge test group) or saline (placebo group). Oxytocin at 5 international units/500 mL Ringer lactate was infused at a rate of 12 mL/h and doubled every 10 minutes until it induced three uterine contractions per 10-minute interval, at which point the oxytocin administration was discontinued.

Arterial cord blood samples were collected immediately after delivery into ethylenediamine pentaacetic acid tubes, centrifuged, and the plasma was stored at −80°C. Copeptin was measured in three batches using the BRAHMS KRYPTOR automated research sandwich immunoluminometric assay, as described previously.[5] Delay in introducing the latest and highly sensitive BRAHMS copeptin assay onto the Swiss market led to an enrollment gap of 1 year, because our aim was to measure all batches with the new assay, including the samples from the first enrollment period.

Neonatal copeptin levels were the primary endpoint. Secondary endpoints included biochemical and physiologic parameters of fetal and maternal well-being, in particular respiratory morbidity, oxytocin challenge test acceptability, and the noncontinuation of labor postoxytocin challenge test. We performed all statistical analyses in STATA 10.1 using the Mann-Whitney test and χ^2 test or Fisher exact test as appropriate to compare groups at a 95% significance level.

According to the interim analysis after enrolling 30 patients per group, the sample size was set to 70 per group with a 10% sample error rate, which would allow us to detect a difference in copeptin concentrations of 21 pmol/L (from 9 to 30 pmol/L) with α of 0.05 and power of 90%.

RESULTS

From January 2012 to October 2012 and from September 2013 to January 2015, 78 women underwent an oxytocin challenge test and 78 placebo infusion, of whom 12 and 11, respectively, were excluded as a result of insufficient blood sample volume for analysis (Fig. 1). Indications for elective cesarean delivery were previous delivery and cesarean delivery on demand. Mean maternal age, maternal parity, rate of previous cesarean delivery, and neonatal sex were similar in both groups (Table 1).

The time interval between discontinuation of the oxytocin challenge test infusion and delivery was 71 (28–342) minutes [median (range)]. Umbilical cord plasma copeptin concentrations were significantly higher in the oxytocin challenge test group: 22.15 (3.22–2,319) compared with 7.39 (2.47–344) pmol/L ($P<.001$; [median (range)]) (Fig. 2).

In no case did the oxytocin challenge test have to be interrupted because of painful contractions or a nonreassuring fetal heart rate pattern nor did labor continue after the oxytocin challenge test was stopped.

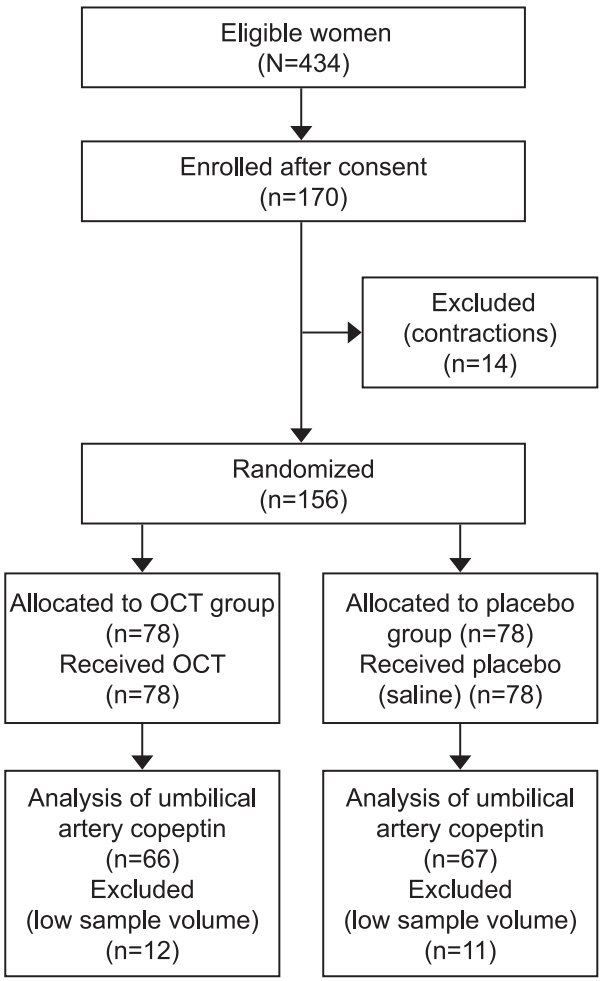

Fig. 1. Study design and enrollment. OCT, oxytocin challenge test.

Wellmann. Copeptin Response to Oxytocin Challenge. Obstet Gynecol 2016.

Table 1. Baseline Characteristics and Neonatal Outcome Parameters of the Oxytocin Challenge and Placebo Groups

Variable	Oxytocin Challenge (n=66)	Placebo (n=67)	*P*
Maternal age (y)	33.7±5.0	33.5±5.9	
Multiparous	40 (61)	46 (69)	
Race			
White	60 (91)	56 (84)	
Other	6 (9)	11 (16)	
Indications for cesarean delivery			
Previous cesarean delivery	33 (50)	39 (58)	
Cesarean delivery on demand	30 (45.5)	23 (34)	
Other*	3 (4.5)	5 (8)	
Gestational age (d)	270.5±5.0	269.3±4.4	
Birth weight (g)	3,349±470	3,264±478	
Birth weight percentile	59.4±29.1	56.1±29.6	
Neonatal sex			
Female	31 (47)	39 (58)	
Male	35 (53)	28 (42)	
Umbilical artery pH	7.32±0.06	7.33±0.04	.71
Umbilical artery lactate (mmol/L)	2.15±0.74	2.18±0.6	.80
5-min Apgar score	9.1±0.4	9.0±0.5	.32
Respiratory distress	2 (3)	4 (6)	.41†
Postnatal neonatal weight loss (%)	7.2±2.3	7.2±2.0	1.0

Data are mean±standard deviation or n (%) unless otherwise specified.

* Retinopathy, spondylopathy, previous third-degree perineal tear, urinary incontinence, estimated fetal weight greater than the 95th percentile.

Data were compared using Student *t* test for continuous data and χ^2 test or †Fisher exact test for categorical data.

No neonate in either group showed signs of asphyxia; there were no instances of low umbilical artery pH, low Apgar score, or elevated umbilical artery lactate (Table 1). Only 36 of 66 (55%) women in the oxytocin challenge test group noticed the contractions.

DISCUSSION

The main finding of this randomized trial is that copeptin, a surrogate marker of plasma vasopressin, is markedly increased in the umbilical cord blood of neonates exposed to oxytocin challenge test-induced contractions before elective cesarean delivery. The threefold difference compared with the placebo group was unassociated with any evidence of acidosis.

Unexpectedly, plasma copeptin levels were spread over a wide range in both groups (Fig. 2). Even a few control neonates had fairly high copeptin levels, perhaps as a result of unrecognized contractions before enrollment. This possibility is supported by the fact that only half the women in the oxytocin challenge test group noticed their oxytocin challenge test-induced contractions.

Mild uterine contractions lead to brief pO_2 drops in the fetus, often without noticeable changes in fetal heart rate tracing.[13–15] Animal data indicate a direct and dose-dependent link between uterine contractions and fetal arterial pO_2 changes[16,17] and a relationship between arterial pO_2 and plasma AVP in fetal sheep.[18,19] Even changes in fetal arterial pO_2 as small as 2.5 mm Hg were sufficient to release corticotropin, an effector hormone of AVP and corticotropin-releasing hormone.[20] However, it remains open whether such a link among mild uterine contractions, fetal pO_2 changes, and copeptin–AVP release might explain our observations reported here.

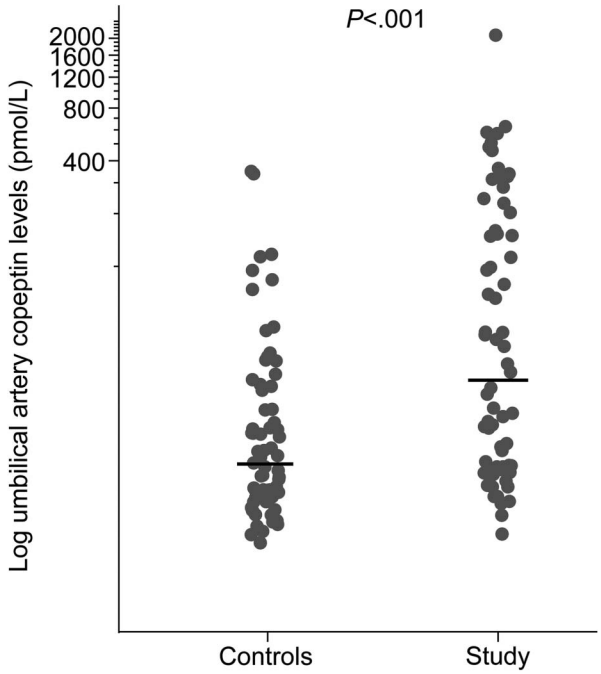

Fig. 2. Logarithmic median copeptin levels in umbilical cord blood from neonates in the oxytocin challenge and placebo groups. $P<.001$, Mann-Whitney test.

Wellmann. Copeptin Response to Oxytocin Challenge. Obstet Gynecol 2016.

Copeptin reflects vasopressin secretion. Animal studies suggest that vasopressin regulates lung fluid secretion and reabsorption.[21–23] However, the mechanism involved remains uncertain. In fetal sheep, Albuquerque et al[24] found no evidence that the vasopressin-2 receptor mediated a reduction in lung fluid production; they suggested the effect was instead mediated by the vasopressin-1 receptor. In the neonatal rat, on the other hand, Guetta et al[25] showed that the vasopressin-2 receptor regulates the increase in active sodium transport and alveolar fluid clearance from the lung.

Compared with vaginal birth or cesarean delivery after the onset of labor, elective cesarean delivery performed before the onset of labor and rupture of the membranes carries an increased risk of neonatal respiratory morbidity such as respiratory distress syndrome or transient tachypnea.[26–28] Hence, it has been proposed that corticosteroids be administered (prophylactically) between 37 and 38 weeks of gestation before term elective cesarean delivery to reduce neonatal respiratory morbidity.[29,30] Despite the evidence of respiratory benefit[29–31] and the absence, as far as is known, of adverse long-term outcomes,[32] serious reservations persist.[33,34]

The present study was powered for the primary endpoint, namely copeptin at birth. None of the results for parameters of fetal or maternal well-being were significant. Thus, no conclusions can be drawn on the secondary endpoint of respiratory morbidity. However, the excellent acceptance of the oxytocin challenge test and the absence of safety issues in this trial, in particular that labor did not progress after withdrawal of oxytocin infusion, favor the project of a larger trial geared to neonatal respiratory morbidity as the primary endpoint. A power calculation based on the observed proportions of respiratory morbidity revealed that a sample size of 1,000 cases and 1,000 controls would be necessary to detect a clinically relevant difference with 90% power, that is, a reduction in neonatal respiratory morbidity from a rate of 6% to 3%.

The oxytocin challenge test has been a standard procedure for many decades in pregnancies with suspected placental insufficiency, but to our knowledge, we are the first to perform a study investigating the effect of an oxytocin challenge test on an appropriately grown fetus shortly before elective cesarean delivery (search was conducted on MEDLINE, available through PubMed to December 2015 with the following search terms: oxytocin challenge, cesarean). We hypothesize that the mild uterine contractions induced by the oxytocin challenge test suffice to upregulate a variety of stress hormones in the fetus, principally corticosteroids, that may help to improve primary adaptation to an air-breathing environment. More particularly, there is evidence that AVP itself, which we measured using its surrogate marker copeptin, specifically supports adaptation of the lung, including alveolar fluid reabsorption and surfactant secretion.[21,35,36]

In conclusion, oxytocin challenge test-induced contractions suffice to elevate fetal levels of copeptin and inferentially those of AVP. This result is an argument in favor of a trial designed to lower neonatal respiratory morbidity after elective cesarean delivery by a preemptive intervention that increases fetal copeptin levels.

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